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*[Continued on next page]*

(54) Title: TRANSGENIC MICE CONTAINING TARGETED GENE DISRUPTIONS

(57) Abstract: The present invention relates to transgenic animals, as well as compositions and methods relating to the characterization of gene function. Specifically, the present invention provides transgenic mice comprising mutations in a GPCR gene. Such transgenic mice are useful as models for disease and for identifying agents that modulate gene expression and gene function, and as potential treatments for various disease states and disease conditions.

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We claim:

1. A targeting construct comprising:

   (a) a first polynucleotide sequence homologous to a target gene selected from the group consisting of: a melanocortin-3 gene, a 5-HT-2B gene, a chemokine receptor 9A gene, a glucocorticoid-induced receptor gene, an orphan GPR10 (UHR-1) gene, an orphan GPR14 gene, an orphan GPR15 gene, a beta chemokine receptor (E01) gene, an endothelial differentiation GPCR 3 (EDG3) gene, an ATP receptor P2U1gene, and an adenosine 3 receptor gene;

   (b) a second polynucleotide sequence homologous to the target gene; and

   (c) a selectable marker.

2. The targeting construct of claim 1, wherein the targeting construct further comprises a screening marker.

3. A method of producing a targeting construct for a target gene selected from the group consisting of a melanocortin-3 gene, a 5-HT-2B gene, a chemokine receptor 9A gene, a glucocorticoid-induced receptor gene, an orphan GPR10 (UHR-1) gene, an orphan GPR14 gene, an orphan GPR15 gene, a beta chemokine receptor (E01) gene, an endothelial differentiation GPCR 3 (EDG3) gene, an ATP receptor P2U1gene, and an adenosine 3 receptor gene, the method comprising:

   (a) obtaining a first polynucleotide sequence homologous to the target gene;

   (b) obtaining a second polynucleotide sequence homologous to the target gene;

   (c) providing a vector comprising a selectable marker; and

   (d) inserting the first and second sequences into the vector, to produce the targeting construct.

4. A method of producing a targeting construct for a target gene selected from the group consisting of: a melanocortin-3 gene, a 5-HT-2B gene, a chemokine receptor 9A gene, a glucocorticoid-induced receptor gene, an orphan GPR10 (UHR-1) gene, an orphan GPR14 gene, an orphan GPR15 gene, a beta chemokine receptor (E01) gene, an endothelial differentiation GPCR 3 (EDG3) gene, an ATP receptor P2U1gene, and an adenosine 3 receptor gene, the method comprising:

   (a) providing a polynucleotide comprising a first sequence homologous to a first region of the target gene and a second sequence homologous to a second region of the target gene; and

   (b) inserting a positive selection marker between the first and second sequences to form the targeting construct.

5. A cell comprising a disruption in a target gene selected from the group consisting of: a melanocortin-3 gene, a 5-HT-2B gene, a chemokine receptor 9A gene, a glucocorticoid-induced receptor gene, an orphan GPR10 (UHR-1) gene, an orphan GPR14 gene, an orphan GPR15 gene,

a beta chemokine receptor (E01) gene, an endothelial differentiation GPCR 3 (EDG3) gene, an ATP receptor P2U1gene, and an adenosine 3 receptor gene.

6. The cell of claim 5, wherein the cell is a murine cell.
7. The cell of claim 6, wherein the murine cell is an embryonic stem cell.
8. A non-human transgenic animal comprising a disruption in a target gene selected from the group consisting of: a melanocortin-3 gene, a 5-HT-2B gene, a chemokine receptor 9A gene, a glucocorticoid-induced receptor gene, an orphan GPR10 (UHR-1) gene, an orphan GPR14 gene, an orphan GPR15 gene, a beta chemokine receptor (E01) gene, an endothelial differentiation GPCR 3 (EDG3) gene, an ATP receptor P2U1gene, and an adenosine 3 receptor gene.
9. A cell derived from the non-human transgenic animal of claim 8.
10. A method of producing a transgenic mouse, the method comprising:
    (a) introducing the targeting construct of claim 1 into a cell;
    (b) introducing the cell into a blastocyst;
    (c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and
    (d) breeding the chimeric mouse to produce the transgenic mouse.
11. A method of identifying an agent that modulates the expression of a target gene selected from the group consisting of: a melanocortin-3 gene, a 5-HT-2B gene, a chemokine receptor 9A gene, a glucocorticoid-induced receptor gene, an orphan GPR10 (UHR-1) gene, an orphan GPR14 gene, an orphan GPR15 gene, a beta chemokine receptor (E01) gene, an endothelial differentiation GPCR 3 (EDG3) gene, an ATP receptor P2U1gene, and an adenosine 3 receptor gene, the method comprising:
    (a) providing a non-human transgenic animal comprising a disruption in the target gene;
    (b) administering an agent to the non-human transgenic animal; and
    (c) determining whether the expression of the disrupted target gene in the non-human transgenic animal is modulated.
12. A method of identifying an agent that modulates the function of a target gene selected from the group consisting of a melanocortin-3 gene, a 5-HT-2B gene, a chemokine receptor 9A gene, a glucocorticoid-induced receptor gene, an orphan GPR10 (UHR-1) gene, an orphan GPR14 gene, an orphan GPR15 gene, a beta chemokine receptor (E01) gene, an endothelial differentiation GPCR 3 (EDG3) gene, an ATP receptor P2U1gene, and an adenosine 3 receptor gene, the method comprising:
    (a) providing a non-human transgenic animal comprising a disruption in the target gene;
    (b) administering an agent to the non-human transgenic animal; and

(c) determining whether the function of the disrupted target gene in the non-human transgenic animal is modulated.

13. A method of identifying an agent that modulates the expression of a target gene selected from the group consisting of: a melanocortin-3 gene, a 5-HT-2B gene, a chemokine receptor 9A gene, a glucocorticoid-induced receptor gene, an orphan GPR10 (UHR-1) gene, an orphan GPR14 gene, an orphan GPR15 gene, a beta chemokine receptor (E01) gene, an endothelial differentiation GPCR 3 (EDG3) gene, an ATP receptor P2U1gene, and an adenosine 3 receptor gene, the method comprising:

(a) providing a cell comprising a disruption in the target gene;

(b) contacting the cell with an agent; and

(c) determining whether expression of the target gene is modulated.

14. A method of identifying an agent that modulates the function of a target gene selected from the group consisting of: a melanocortin-3 gene, a 5-HT-2B gene, a chemokine receptor 9A gene, a glucocorticoid-induced receptor gene, an orphan GPR10 (UHR-1) gene, an orphan GPR14 gene, an orphan GPR15 gene, a beta chemokine receptor (E01) gene, an endothelial differentiation GPCR 3 (EDG3) gene, an ATP receptor P2U1gene, and an adenosine 3 receptor gene, the method comprising:

(a) providing a cell comprising a disruption in the target gene;

(b) contacting the cell with an agent; and

(c) determining whether the function of the target gene is modulated.

15. The method of claim 13 or claim 14, wherein the cell is derived from the non-human transgenic animal of claim 8.

16. An agent identified by the method of claim 11, claim 12, claim 13, or claim 14.

17. A targeting construct comprising:

(a) a first polynucleotide sequence homologous to a melanocortin-3 receptor gene;

(b) a second polynucleotide sequence homologous to the melanocortin-3 receptor gene; and

(c) a selectable marker.

18. The targeting construct of claim 17, wherein the targeting construct further comprises a screening marker.

19. A method of producing a targeting construct, the method comprising:

(a) providing a first polynucleotide sequence homologous to a melanocortin-3 receptor gene;

(b) providing a second polynucleotide sequence homologous to the melanocortin-3 receptor;

(c) providing a selectable marker; and

(d) inserting the first sequence, second sequence, and selectable marker into a vector, to produce the targeting construct.

20. A method of producing a targeting construct, the method comprising:

(a) providing a polynucleotide comprising a first sequence homologous to a first region of a melanocortin-3 receptor gene and a second sequence homologous to a second region of a melanocortin-3 receptor gene;

(b) inserting a positive selection marker in between the first and second sequences to form the targeting construct.

21. A cell comprising a disruption in a melanocortin-3 receptor gene.

22. The cell of claim 21, wherein the cell is a murine cell.

23. The cell of claim 22, wherein the murine cell is an embryonic stem cell.

24. A non-human transgenic animal comprising a disruption in a melanocortin-3 receptor gene.

25. A cell derived from the non-human transgenic animal of claim 24.

26. A method of producing a transgenic mouse comprising a disruption in a melanocortin-3 receptor gene, the method comprising:

(a) introducing the targeting construct of claim 17 into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse.

27. A method of identifying an agent that modulates the expression of a melanocortin-3 receptor, the method comprising:

(a) providing a non-human transgenic animal comprising a disruption in a melanocortin-3 receptor gene;

(b) administering an agent to the non-human transgenic animal; and

(c) determining whether the expression of melanocortin-3 receptor in the non-human transgenic animal is modulated.

28. A method of identifying an agent that modulates the function of a melanocortin-3 receptor, the method comprising:

(a) providing a non-human transgenic animal comprising a disruption in a melanocortin-3 receptor gene;

(b) administering an agent to the non-human transgenic animal; and

(c) determining whether the function of the disrupted melanocortin-3 receptor gene in the non-human transgenic animal is modulated.

29. A method of identifying an agent that modulates the expression of melanocortin-3 receptor, the method comprising:
    (a) providing a cell comprising a disruption in a melanocortin-3 receptor gene;
    (b) contacting the cell with an agent; and
    (c) determining whether expression of the melanocortin-3 receptor is modulated.
30. A method of identifying an agent that modulates the function of a melanocortin-3 receptor gene, the method comprising:
    (a) providing a cell comprising a disruption in a melanocortin-3 receptor gene;
    (b) contacting the cell with an agent; and
    (c) determining whether the function of the melanocortin-3 receptor gene is modulated.
31. The method of claim 29 or claim 30, wherein the cell is derived from the non-human transgenic animal of claim 24.
32. An agent identified by the method of claim 27, claim 28, claim 29, or claim 30.
33. A transgenic mouse comprising a disruption in a melanocortin-3 receptor gene, wherein the transgenic mouse exhibits at least one of the following phenotypes: a kidney abnormality or a behavioral abnormality.
34. The transgenic mouse of claim 33, wherein the kidney abnormality is absence of one kidney.
35. The transgenic mouse of claim 33, wherein the kidney abnormality is reduced size of the kidney relative to a wild-type mouse.
36. The transgenic mouse of claim 33, wherein the kidney comprises unilateral renal agenesis.
37. The transgenic mouse of claim 33, wherein the behavioral abnormality is passivity.
38. The transgenic mouse of claim 33, wherein the behavioral abnormality is hypoactivity.
39. The transgenic mouse of claim 33, wherein the behavioral abnormality is decreased locomotion.
40. The transgenic mouse of claim 33, wherein the behavioral abnormality is a decrease in the attempt to escape while being examined relative to a wild type mouse.
41. The transgenic mouse of claim 33, wherein the behavioral abnormality is absence of any attempt to escape while being examined.
42. The transgenic mouse of claim 33, wherein the behavioral abnormality is observed in males.
43. A method of producing a transgenic mouse comprising a disruption in a melanocortin-3 receptor gene, wherein the transgenic mouse exhibits at least one of the following phenotypes: a kidney abnormality or a behavioral abnormality, the method comprising:
    (a) introducing a melanocortin-3 receptor gene targeting construct into a cell;
    (b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse comprising a disruption in a melanocortin-3 receptor gene.

44. A transgenic mouse produced by the method of claim 43.

45. A cell derived from the transgenic mouse of claim 33 or claim 44.

46. A method of identifying an agent that ameliorates a phenotype associated with a disruption in a melanocortin-3 receptor gene, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in a melanocortin-3 receptor gene; and

(b) determining whether the agent ameliorates at least one of the following phenotypes: a kidney abnormality or a behavioral abnormality.

47. A method of identifying an agent that modulates melanocortin-3 receptor expression, the method comprising:

(a) administering an agent to the transgenic mouse comprising a disruption in a melanocortin-3 receptor gene; and

(b) determining whether the agent modulates melanocortin-3 receptor expression in the transgenic mouse, wherein the agent has an effect on at least one of the following behaviors: passivity, locomotion or attempts to escape while being examined.

48. A method of identifying an agent that modulates a behavior associated with a disruption in a melanocortin-3 receptor gene, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in a melanocortin-3 receptor gene; and

(b) determining whether the agent modulates passivity, locomotion or attempts to escape while being examined.

49. A method of identifying an agent that modulates melanocortin-3 receptor gene function, the method comprising:

(a) providing a cell comprising a disruption in a melanocortin-3 receptor gene;

(b) contacting the cell with an agent; and

(c) determining whether the agent modulates melanocortin-3 receptor gene function, wherein the agent modulates a phenotype associated with a disruption in a melanocortin-3 receptor gene.

50. The method of claim 49, wherein the phenotype comprises at least one of the following: a kidney abnormality or a behavioral abnormality.

51. An agent identified by the method of claim 46, claim 47, claim 48, or claim 49.

52. An agonist or antagonist of a melanocortin-3 receptor.

53. A targeting construct comprising:

(a) a first polynucleotide sequence homologous to a 5-HT-2B gene;

(b) a second polynucleotide sequence homologous to the 5-HT-2B gene; and

(a) a selectable marker.

54. The targeting construct of claim 53, wherein the targeting construct further comprises a screening marker.

55. A method of producing a targeting construct, the method comprising:

(a) providing a first polynucleotide sequence homologous to a 5-HT-2B gene;

(b) providing a second polynucleotide sequence homologous to the 5-HT-2B ;

(c) providing a selectable marker; and

(d) inserting the first sequence, second sequence, and selectable marker into a vector, to produce the targeting construct.

56. A method of producing a targeting construct, the method comprising:

(a) providing a polynucleotide comprising a first sequence homologous to a first region of a 5-HT-2B gene and a second sequence homologous to a second region of a 5-HT-2B gene;

(b) inserting a positive selection marker in between the first and second sequences to form the targeting construct.

57. A cell comprising a disruption in a 5-HT-2B gene.

58. The cell of claim 57, wherein the cell is a murine cell.

59. The cell of claim 58, wherein the murine cell is an embryonic stem cell.

60. A non-human transgenic animal comprising a disruption in a 5-HT-2B gene.

61. A cell derived from the non-human transgenic animal of claim 60.

62. A method of producing a transgenic mouse comprising a disruption in a 5-HT-2B gene, the method comprising:

(a) introducing the targeting construct of claim 53 into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse.

63. A method of identifying an agent that modulates the expression of a 5-HT-2B, the method comprising:

(a) providing a non-human transgenic animal comprising a disruption in a 5-HT-2B gene;

(b) administering an agent to the non-human transgenic animal; and

(c) determining whether the expression of 5-HT-2B in the non-human transgenic animal is modulated.

64. A method of identifying an agent that modulates the function of a 5-HT-2B, the method comprising:

(a) providing a non-human transgenic animal comprising a disruption in a 5-HT-2B gene;

(b) administering an agent to the non-human transgenic animal; and

(c) determining whether the function of the disrupted 5-HT-2B gene in the non-human transgenic animal is modulated.

65. A method of identifying an agent that modulates the expression of 5-HT-2B, the method comprising:

i) providing a cell comprising a disruption in a 5-HT-2B gene;

(b) contacting the cell with an agent; and

(c) determining whether expression of the 5-HT-2B is modulated.

66. A method of identifying an agent that modulates the function of a 5-HT-2B gene, the method comprising:

(a) providing a cell comprising a disruption in a 5-HT-2B gene;

(b) contacting the cell with an agent; and

(c) determining whether the function of the 5-HT-2B gene is modulated.

67. The method of claim 65 or claim 66, wherein the cell is derived from the non-human transgenic animal of claim 60.

68. An agent identified by the method of claim 63, claim 64, claim 65, or claim 66.

69. A transgenic mouse comprising a disruption in a 5-HT-2B gene, wherein the transgenic mouse exhibits at least one of the following phenotypes: embryonic lethality, abnormal embryos, retarded development, and reabsorbed embryos.

70. The transgenic mouse of claim 69, wherein development is arrested at embryonic day 8.5.

71. The transgenic mouse of claim 69, wherein homozygous offspring are undetectable after embryonic day E8.5.

72. The transgenic mouse of claim 69, wherein homozygous embryos die between embryonic day 8.5 and embryonic day 9.5.

73. The transgenic mouse of claim 69, wherein the wherein the embryos are reabsorbed between embryonic day 8.5 and embryonic day 9.5.

74. A method of producing a transgenic mouse comprising a disruption in a 5-HT-2B gene, wherein the transgenic mouse exhibits at least one of the following phenotypes: embryonic lethality, abnormal embryos, retarded development, and reabsorbed embryos, the method comprising:

(a) introducing a 5-HT-2B gene targeting construct into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse comprising a disruption in a 5-HT-2B gene.

75. A transgenic mouse produced by the method of claim 74.

76. A cell derived from the transgenic mouse of claim 60 or claim 75.

77. A method of identifying an agent that ameliorates a phenotype associated with a disruption in a 5-HT-2B gene, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in a 5-HT-2B gene; and

(b) determining whether the agent ameliorates at least one of the following phenotypes: embryonic lethality, abnormal embryos, retarded development, and reabsorbed embryos.

78. An agonist or antagonist of a 5-HT-2B receptor.

79. A targeting construct comprising:

(a) a first polynucleotide sequence homologous to a chemokine receptor 9A gene;

(b) a second polynucleotide sequence homologous to the chemokine receptor 9A gene; and

(c) a selectable marker.

80. The targeting construct of claim 79, wherein the targeting construct further comprises a screening marker.

81. A method of producing a targeting construct, the method comprising:

(a) providing a first polynucleotide sequence homologous to a chemokine receptor 9A gene;

(b) providing a second polynucleotide sequence homologous to the chemokine receptor 9A;

(c) providing a selectable marker; and

(d) inserting the first sequence, second sequence, and selectable marker into a vector, to produce the targeting construct.

82. A method of producing a targeting construct, the method comprising:

(a) providing a polynucleotide comprising a first sequence homologous to a first region of a chemokine receptor 9A gene and a second sequence homologous to a second region of a chemokine receptor 9A gene;

(b) inserting a positive selection marker in between the first and second sequences to form the targeting construct.

83. A cell comprising a disruption in a chemokine receptor 9A gene.

84. The cell of claim 83, wherein the cell is a murine cell.

85. The cell of claim 84, wherein the murine cell is an embryonic stem cell.

86. A non-human transgenic animal comprising a disruption in a chemokine receptor 9A gene.

87. A cell derived from the non-human transgenic animal of claim 86.

88. A method of producing a transgenic mouse comprising a disruption in a chemokine receptor 9A gene, the method comprising:

(a) introducing the targeting construct of claim 79 into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse.

89. A method of identifying an agent that modulates the expression of a chemokine receptor 9A, the method comprising:

(a) providing a non-human transgenic animal comprising a disruption in a chemokine receptor 9A gene;

(b) administering an agent to the non-human transgenic animal; and

(c) determining whether the expression of chemokine receptor 9A in the non-human transgenic animal is modulated.

90. A method of identifying an agent that modulates the function of a chemokine receptor 9A, the method comprising:

(a) providing a non-human transgenic animal comprising a disruption in a chemokine receptor 9A gene;

(b) administering an agent to the non-human transgenic animal; and

(c) determining whether the function of the disrupted chemokine receptor 9A gene in the non-human transgenic animal is modulated.

91. A method of identifying an agent that modulates the expression of chemokine receptor 9A, the method comprising:

(a) providing a cell comprising a disruption in a chemokine receptor 9A gene;

(b) contacting the cell with an agent; and

(c) determining whether expression of the chemokine receptor 9A is modulated.

92. A method of identifying an agent that modulates the function of a chemokine receptor 9A gene, the method comprising:

(a) providing a cell comprising a disruption in a chemokine receptor 9A gene;

(b) contacting the cell with an agent; and

(c) determining whether the function of the chemokine receptor 9A gene is modulated.

93. The method of claim 91 or claim 92, wherein the cell is derived from the non-human transgenic animal of claim 86.

94. An agent identified by the method of claim 89, claim 90, claim 91, or claim 92.

95. A transgenic mouse comprising a disruption in a chemokine receptor 9A gene, wherein the transgenic mouse exhibits at least one of the following phenotypes: decreased agility, coordination, or balance relative to a wild-type mouse.

96. The transgenic mouse of claim 95, wherein decreased agility, coordination, or balance is characterized by decreased performance on an accelerating rotarod.

97. The transgenic mouse of claim 95, wherein decreased agility, coordination, or balance is characterized by falling from an accelerating rotarod at lower speeds relative to a wild-type mouse.

98. A method of producing a transgenic mouse comprising a disruption in a chemokine receptor 9A gene, wherein the transgenic mouse exhibits at least one of the following phenotypes: decreased agility, coordination, or balance relative to a wild-type mouse, the method comprising:

(a) introducing a chemokine receptor 9A gene targeting construct into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse comprising a disruption in a chemokine receptor 9A gene.

99. A transgenic mouse produced by the method of claim 98.

100. A cell derived from the transgenic mouse of claim 95 or claim 98.

101. A method of identifying an agent that ameliorates a phenotype associated with a disruption in a chemokine receptor 9A gene, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in a chemokine receptor 9A gene; and

(b) determining whether the agent ameliorates at least one of the following phenotypes: decreased agility, coordination, or balance relative to a wild-type mouse.

102. A method of identifying an agent that modulates chemokine receptor 9A expression, the method comprising:

(a) administering an agent to the transgenic mouse comprising a disruption in a chemokine receptor 9A gene; and

(b) determining whether the agent modulates chemokine receptor 9A expression in the transgenic mouse, wherein the agent has an effect on at least one of the following behaviors: decreased agility, coordination, or balance relative to a wild-type mouse.

103. A method of identifying an agent that modulates a behavior associated with a disruption in a chemokine receptor 9A gene, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in a chemokine receptor 9A gene; and

(b) determining whether the agent modulates agility, coordination, or balance of the transgenic mouse.

104. A method of identifying an agent that modulates chemokine receptor 9A gene function, the method comprising:

(a) providing a cell comprising a disruption in a chemokine receptor 9A gene;

(b) contacting the cell with an agent; and

(c) determining whether the agent modulates chemokine receptor 9A gene function, wherein the agent modulates a phenotype associated with a disruption in a chemokine receptor 9A gene.

105. The method of claim 104, wherein the phenotype comprises at least one of the following: decreased agility, coordination, or balance relative to a wild-type mouse.

106. An agent identified by the method of claim 101, claim 102, claim 103, or claim 104.

107. An agonist or antagonist of a chemokine receptor 9A receptor.

108. Phenotypic data associated with the transgenic mouse of claim 95 or claim 98, wherein the data is in a database.

109. A targeting construct comprising:

(a) a first polynucleotide sequence homologous to a glucocorticoid-induced receptor gene;

(b) a second polynucleotide sequence homologous to the glucocorticoid-induced receptor gene; and

(c) a selectable marker.

110. The targeting construct of claim 111, wherein the targeting construct further comprises a screening marker.

111. A method of producing a targeting construct, the method comprising:

(a) providing a first polynucleotide sequence homologous to a glucocorticoid-induced receptor gene;

(b) providing a second polynucleotide sequence homologous to the glucocorticoid-induced receptor;

(c) providing a selectable marker; and

(d) inserting the first sequence, second sequence, and selectable marker into a vector, to produce the targeting construct.

112. A method of producing a targeting construct, the method comprising:

(a) providing a polynucleotide comprising a first sequence homologous to a first region of a glucocorticoid-induced receptor gene and a second sequence homologous to a second region of a glucocorticoid-induced receptor gene;

(b) inserting a positive selection marker in between the first and second sequences to form the targeting construct.

113. A cell comprising a disruption in a glucocorticoid-induced receptor gene.

114. The cell of claim 113, wherein the cell is a murine cell.

115. The cell of claim 114, wherein the murine cell is an embryonic stem cell.

116. A non-human transgenic animal comprising a disruption in a glucocorticoid-induced receptor gene.

117. A cell derived from the non-human transgenic animal of claim 116.

118. A method of producing a transgenic mouse comprising a disruption in a glucocorticoid-induced receptor gene, the method comprising:

(a) introducing the targeting construct of claim 111 into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse.

119. A method of identifying an agent that modulates the expression of a glucocorticoid-induced receptor, the method comprising:

(a) providing a non-human transgenic animal comprising a disruption in a glucocorticoid-induced receptor gene;

(b) administering an agent to the non-human transgenic animal; and

(c) determining whether the expression of glucocorticoid-induced receptor in the non-human transgenic animal is modulated.

120. A method of identifying an agent that modulates the function of a glucocorticoid-induced receptor, the method comprising:

(a) providing a non-human transgenic animal comprising a disruption in a glucocorticoid-induced receptor gene;

(b) administering an agent to the non-human transgenic animal; and

(c) determining whether the function of the disrupted glucocorticoid-induced receptor gene in the non-human transgenic animal is modulated.

121. A method of identifying an agent that modulates the expression of glucocorticoid-induced receptor, the method comprising:

(a) providing a cell comprising a disruption in a glucocorticoid-induced receptor gene;

(b) contacting the cell with an agent; and

(c) determining whether expression of the glucocorticoid-induced receptor is modulated.

122. A method of identifying an agent that modulates the function of a glucocorticoid-induced receptor gene, the method comprising:

(a) providing a cell comprising a disruption in a glucocorticoid-induced receptor gene;

(b) contacting the cell with an agent; and

(c) determining whether the function of the glucocorticoid-induced receptor gene is modulated.

123. The method of claim 121 or claim 122, wherein the cell is derived from the non-human transgenic animal of claim 116.

124. An agent identified by the method of claim 119, claim 120, claim 121 or claim 122.

125. A transgenic mouse comprising a disruption in a glucocorticoid-induced receptor gene, wherein the transgenic mouse exhibits at least one of the following phenotypes: hyperactivity, reduced anxiety, decreased propensity toward behavioral despair, or decreased propensity toward depression.

126. The transgenic mouse of claim 125, wherein hyperactivity is characterized by an increase in total distance traveled in an open field test, relative to a wild-type mouse.

127. The transgenic mouse of claim 125, wherein hyperactivity is characterized by an increase in the percent of time spent in the central region of the test chamber in an open field test, relative to a wild-type mouse.

128. The transgenic mouse of claim 125, wherein reduced anxiety is characterized by an increase in total distance traveled in an open field test, relative to a wild-type mouse.

129. The transgenic mouse of claim 125, wherein reduced anxiety is characterized by an increase in the percent of time spent in the central region of the test chamber in an open field test, relative to a wild-type mouse.

130. The transgenic mouse of claim 125, wherein the decreased propensity toward behavioral despair is characterized by less time immobile in a tail suspension test relative to a wild-type mouse.

131. The transgenic mouse of claim 125, decreased propensity toward depression is characterized by less time immobile in a tail suspension test relative to a wild-type mouse.

132. A method of producing a transgenic mouse comprising a disruption in a glucocorticoid-induced receptor gene, wherein the transgenic mouse exhibits at least one of the following phenotypes: hyperactivity, reduced anxiety, a decreased propensity toward behavioral despair, or a decreased propensity toward depression, the method comprising:

(a) introducing a glucocorticoid-induced receptor gene targeting construct into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse comprising a disruption in a glucocorticoid-induced receptor gene.

133. A transgenic mouse produced by the method of claim 132.

134. A cell derived from the transgenic mouse of claim 125 or claim 133.

135. A method of identifying an agent that ameliorates a phenotype associated with a disruption in a glucocorticoid-induced receptor gene, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in a glucocorticoid-induced receptor gene; and

(b) determining whether the agent ameliorates at least one of the following phenotypes: hyperactivity, reduced anxiety, decreased propensity toward behavioral despair, or decreased propensity toward depression.

136. A method of identifying an agent that modulates glucocorticoid-induced receptor expression, the method comprising:

(a) administering an agent to the transgenic mouse comprising a disruption in a glucocorticoid-induced receptor gene; and

(b) determining whether the agent modulates glucocorticoid-induced receptor expression in the transgenic mouse, wherein the agent has an effect on at least one of the following behaviors: hyperactivity, anxiety, behavioral despair, or depression.

137. A method of identifying an agent that modulates a behavior associated with a disruption in a glucocorticoid-induced receptor gene, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in a glucocorticoid-induced receptor gene; and

(b) determining whether the agent modulates hyperactivity, anxiety, behavioral despair, or depression.

138. A method of identifying an agent that modulates glucocorticoid-induced receptor gene function, the method comprising:

(a) providing a cell comprising a disruption in a glucocorticoid-induced receptor gene;

(b) contacting the cell with an agent; and

(c) determining whether the agent modulates glucocorticoid-induced receptor gene function, wherein the agent modulates a phenotype associated with a disruption in a glucocorticoid-induced receptor gene.

139. The method of claim 138, wherein the phenotype comprises at least one of the following: hyperactivity, reduced anxiety, decreased propensity toward behavioral despair, or decreased propensity toward depression.

140. An agent identified by the method of claim 135, claim 136, claim 137, or claim 138.

141. A transgenic mouse comprising a disruption in a glucocorticoid-induced receptor gene, wherein the transgenic mouse exhibits hyperactivity, reduced anxiety, a decreased propensity toward behavioral despair, or a decreased propensity toward depression relative to a wild-type mouse.

142. An agonist or antagonist of a glucocorticoid-induced receptor.

143. Phenotypic data associated with the transgenic mouse of claim 125 or claim 133, wherein the data is in a database.